Two Pediatric Cases of Variant Neurogenic Stress Cardiomyopathy After Intracranial Hemorrhage

abstract

Takotsubo cardiomyopathy, also known as stress-induced cardiomyopathy, is an acquired form of left ventricular systolic dysfunction seen in the setting of physiologic stress and the absence of coronary artery disease. It is thought to be caused by excessive sympathetic stimulation. It is well described in the adult literature associated with subarachnoid hemorrhage where it is known as neurogenic stress cardiomyopathy (NSC), but few such pediatric cases have been reported. We describe our experience with 2 children (13- and 10-year-old girls) who presented with spontaneous intracranial hemorrhage followed by pulmonary edema and shock. Echocardiography revealed similar patterns of left ventricular wall motion abnormalities consistent with NSC, inverted Takotsubo variant. One child progressed to death, whereas the other made a remarkable recovery, including significant improvement in cardiac function over the course of 1 week. We argue that at least 1 of these cases represents true stress-induced cardiomyopathy. This report will alert pediatricians to this transient cardiomyopathy that is likely underdiagnosed in pediatric intensive care. We also highlight the challenges of managing both shock and elevated intracranial pressure in the setting of NSC. Pediatrics 2014;134:e1211–e1217
Stress-induced cardiomyopathy (SIC) is a rare disorder described classically in postmenopausal women. It is almost never seen in children. There are a few pediatric case reports describing such cardiomyopathies, but only 1 case was associated with acute neurologic injury. In this setting, it is known as neurogenic stress cardiomyopathy (NSC). Here we discuss 2 cases of spontaneous intracranial hemorrhage and strikingly similar variants of NSC seen within a single year at our PICU.

CASE 1

A healthy 13-year-old girl was found unresponsive at home. She was endotracheally intubated by emergency medical services (EMS) and brought to a local emergency department (ED) where a noncontrast head computed tomography (CT) scan revealed an intracranial mass near the right basal ganglia with old calcifications and acute hemorrhage with early cerebellar tonsillar herniation. She was given mannitol and transported to our level-1 trauma center for neurosurgical care. Soon thereafter she developed pulseless ventricular tachycardia and received 5 minutes of chest compressions, 1 dose of epinephrine, and 1 dose of defibrillation before return of spontaneous circulation. During the code she developed pulmonary edema. A head CT with contrast demonstrated a large, enhancing thalamic mass with severe mass effect. An external ventricular drain (EVD) was emergently placed in the ED. She was admitted to the PICU on phenylephrine and epinephrine infusions to maintain adequate cerebral perfusion pressure (CPP). Further neurosurgical intervention was delayed until her clinical status improved. Three hours after cardiac arrest, electrocardiogram (ECG) demonstrated sinus tachycardia with subtle signs of myocardial ischemia (Fig 1). Troponin-I was elevated at 3.27 ng/mL (normal <0.4). A transthoracic echocardiogram (TTE) obtained 24 hours after cardiac arrest demonstrated normal left ventricular (LV) size, but akinesis of the basal and midventricular segments with mild hypokinesis of the apical segments. Left ventricular ejection fraction (LVEF) was severely depressed at 23% (Fig 2 and Supplemental Videos 1, 2, and 3). On hospital day 4 she tolerated discontinuation of vasopressors. On hospital day 6, troponin-I had normalized. The ST abnormality seen on the previous ECG was no longer present, but there was a persistent deep Q wave in lead aVL. Repeat TTE on hospital day 8 showed improved cardiac function (LVEF 44%) with hypokinesis of midventricular segments and nearly normal apical and basal segments (Fig 3 and Supplemental Videos 4, 5, and 6).

The patient underwent craniotomy with subtotal resection of a grade 1 pilocytic astrocytoma. Soon after surgery, the EVD was removed. On transfer to the rehabilitation service, her only neurologic deficits were mild left-sided hemiparesis and dysphagia with thin liquids. She was discharged to home 13 days after presentation. She has had no cardiac sequelae to date.

CASE 2

A healthy 10-year-old girl presented with sudden headache followed by loss of consciousness. She was endotracheally intubated by EMS and brought to the ED where a noncontrast CT scan revealed an intracranial mass near the right basal ganglia with old calcifications and acute hemorrhage with early cerebellar tonsillar herniation. She was given mannitol and transported to our level-1 trauma center for neurosurgical care. Three hours after cardiac arrest, electrocardiogram (ECG) demonstrated sinus tachycardia with subtle signs of myocardial ischemia (Fig 1). Troponin-I was elevated at 3.27 ng/mL (normal <0.4). A transthoracic echocardiogram (TTE) obtained 24 hours after cardiac arrest demonstrated normal left ventricular (LV) size, but akinesis of the basal and midventricular segments with mild hypokinesis of the apical segments. Left ventricular ejection fraction (LVEF) was severely depressed at 23% (Fig 2 and Supplemental Videos 1, 2, and 3). On hospital day 4 she tolerated discontinuation of vasopressors. On hospital day 6, troponin-I had normalized. The ST abnormality seen on the previous ECG was no longer present, but there was a persistent deep Q wave in lead aVL. Repeat TTE on hospital day 8 showed improved cardiac function (LVEF 44%) with hypokinesis of midventricular segments and nearly normal apical and basal segments (Fig 3 and Supplemental Videos 4, 5, and 6).

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of consciousness and respiratory arrest. She was intubated by EMS and transported to a local ED. ECG rhythm strips done by EMS demonstrated sinus tachycardia with 2-mm ST depression suggestive of inferior wall ischemia. A 12-lead ECG done at the community ED is shown in Fig 4. Chest radiograph revealed pulmonary edema. Noncontrast head CT demonstrated subarachnoid and parenchymal hemorrhages in the left lobe of the cerebellum. She was emergently transported to our level-1 trauma center.

Soon thereafter she developed fluid-refractory shock requiring a nor-epinephrine infusion. CT angiogram demonstrated a ruptured left-sided...
cerebellar arteriovenous fistula with hemorrhage compressing the fourth ventricle. The patient received an emergency craniectomy with EVD. On admission to the PICU, the patient became hypotensive and epinephrine was added. Serum troponin-I level was elevated at 2.55 ng/mL.

On hospital day 2, TTE demonstrated spheroid remodeling of the LV with akinesis of the basal and midventricular segments (Fig 5 and Supplemental Videos 7, 8, 9, 10, and 11). LVEF was severely reduced at 25%. A trial of milrinone, followed by dobutamine, had no benefit.

A repeat ECG on hospital day 3 showed normal sinus rhythm and normalization of the ST segments. Troponin-I was then 0.90 ng/mL.

Throughout her hospitalization, maintaining adequate CPP was extremely difficult despite significant inotropic support.

FIGURE 3
Case 1 follow-up TTE. Various echocardiographic (ECG) views arranged as in Fig 2. The LV is again normal in size and wall thickness. There is isolated mid LV segment hypokinesis with normal apical and basal contractility. LVEF 44%. This is consistent with recovering inverted TC.
support. The patient went on to develop central brain herniation. She died on hospital day 10 after parental consent to organ donation after cardiac death.

DISCUSSION

Takotsubo cardiomyopathy (TC), also called SIC and apical ballooning syndrome, is well described in the adult literature but rarely reported in children. It was first described in 1990 in Japan.2 The syndrome is characterized by transient systolic dysfunction without obstructive coronary artery disease.3 In the “classic” form of TC, there is akinesis of the mid and apical LV segments with sparing of the basal segments, resulting in apical ballooning during systole. The right ventricle is affected in an estimated one-third of cases, and in 1 adult series this was a predictor of adverse outcomes.4 Increasingly, “atypical” forms of TC in which the basal, mid, or apical segments are affected in isolation have been described. Recently, an “inverted TC” has been described in adults in whom there is akinesis of the mid and basal LV segments, similar to the cases described herein, with hyperkinesis of the apex.5 The Mayo Clinic criteria for the diagnosis of SIC recognizes this heterogeneity of wall motion abnormalities.6 In this definition, there is transient hypokinesis, akinesis, or dyskinesis of the LV mid segments with or without apical involvement and the regional wall motion abnormalities must extend beyond a single epicardial coronary distribution. There must be an absence of obstructive coronary artery disease (CAD). There are new ECG abnormalities or modest elevation in cardiac troponin (the peak typically underestimates the degree of wall motion abnormality). Finally, pheochromocytoma and myocarditis must not be present. Notably, intracranial bleeds are not excluded and Prasad et al6 concede that so-called neurogenic stunning is likely a manifestation of the same spectrum of disease. Coronary imaging is necessary for the full diagnosis of SIC, but in patients with a very low likelihood of CAD, TTE may be sufficient.

Classic TC is most common in postmenopausal women. Men account for only ~10% of cases. The mean age in patients with TC is 61 to 76 years.7 TC is present in ~2% of patients presenting with acute coronary syndrome.8 It is surprisingly common in adult ICU patients, as demonstrated in 1 prospective cohort study that evaluated 92 consecutive noncardiac adult ICU patients for TC.9 Of these patients, 28% had TC by hospital day 7, including 23% on admission. The incidence of SIC in the pediatric population is unknown. The underlying pathophysiology is not fully known; however, several lines of evidence suggest that excess circulating catecholamines, both endogenous and exogenous, exert a toxic effect on the susceptible myocardium and the microvascular endothelium.8,10,11

**FIGURE 4**

Case 2 initial 12-lead ECG done in the community ED that is remarkably similar to the initial ECG in case 1 (Fig 1). Sinus tachycardia with 1-mm J-point depression in the inferior leads, V4, and V5. There is an isolated Q wave in lead aVL.
SIC typically resolves within weeks and has a favorable prognosis by itself, thus treatment is supportive. In a hemodynamically stable patient this can include angiotensin-converting enzyme inhibitors, β-blockers, and diuretics. Current research is investigating the possible benefit of early β-blockade. The presence of cardiogenic shock in adults with SIC may require urgent angiography and intra-aortic balloon counterpulsation. There is no established treatment algorithm for children with SIC.

FIGURE 5
Case 2 TTE. Apical 4-chamber view at end-diastole (A) and end-systole (B). Apical 2-chamber view at end-diastole (C) and end-systole (D). Apical long-axis view at end-diastole (E) and end-systole (F). The LV is normal in size and thickness, but demonstrates spheroid remodeling with global hypokinesis and akinesis of the basal and midventricular segments. LVEF 25%. The right heart is normal.
A fascinating brain-heart relationship is well known to neurologic critical care: adult patients with subarachnoid hemorrhage not infrequently meet the diagnostic criteria for SIC. Several authors have suggested that there may be significant overlap between this so-called NSC and SIC in terms of molecular mechanism, wall motion abnormalities, and natural history.12 Our 2 pediatric cases were strikingly similar in terms of presentation and echocardiographic findings. To our knowledge, case 1 is the first reported pediatric case of this cardiomyopathy presenting with ventricular tachycardia arrest. This case meets all diagnostic criteria for SIC except for angiography to rule out CAD. Given the extremely rare prevalence of obstructive CAD in the pediatric population, angiography was not clinically necessary. Furthermore, the drastic improvement in cardiac function after 1 week is in line with the natural history of SIC, not myocardial infarction. In case 2, the echocardiogram demonstrated wall motion abnormalities which were quite similar to the initial study in case 1. Neither repeat TTE nor cardiac autopsy was performed.

We propose that both cases represent an inverted Takotsubo variant of SIC, which could be classified as NSC, given the underlying cause. The clinical resemblance between these 2 cases suggests a common pathophysiologic mechanism and raises an alert about pediatric SIC, which, to date, has been rarely reported and possibly underdiagnosed. Children with any serious illness release endogenous catecholamines that could be cardiotoxic. This downstream effect of subarachnoid hemorrhage, in particular, may be exceptionally deleterious and likely to lead to cardiomyopathy. Supraphysiologic doses of exogenous catecholamine given for shock and to maintain goal CPPs likely play a role as well. The LV basal and mid segments may be preferentially sensitive in young people, leading to the inverted Takotsubo variant of SIC that we describe.

Our experience has implications for pediatricians caring for children with acute brain injury. First, any evidence of myocardial ischemia or heart failure should be evaluated early with echocardiography. Second, treatment of NSC-related shock in a pediatric patient with elevated intracranial pressure presents unique challenges. Achieving a goal CPP often requires the use of vasopressors, yet adrenergic agents might exacerbate myocardial toxicity and worsen or prolong the cardiomyopathy. Conversely, heart failure medications might cause an unacceptable drop in CPP. Future prospective studies in the ICU setting are needed to determine the incidence, unique features, attributable morbidity, and optimal management of pediatric SIC.

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Pediatrics 2014;134:e1211; originally published online September 8, 2014;
DOI: 10.1542/peds.2013-1881

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*Pediatrics* 2014;134;e1211; originally published online September 8, 2014;
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